REMARKS

Claims 1, 4-6, 8, 9, 12, 13, and 39 are pending in this application. No new matter has been added with this amendment. After entry of this Amendment, Claims 1, 4-6, 8, 9, 12, 13, and 39 will be pending in this application.

I. Claim Rejections - 35 USC §112

Claims 1, 4-6, 8, 9, 12, 13 and 39 stand rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

According to the Examiner, the claims are confusing and unclear for the asserted reason that claim 1 recites a bone substitute comprising components a), b) and c) but after component c) is formed, this is the only component present. The Examiner explains that components a) and b) form component c), and components a) and b) no longer exist as separate components after component c) is formed. The Examiner also states that in c) of claim 1, the word "setting" is unclear.

With regard to claims 8 and 9, the Examiner states that it is unclear as to where in claim 1 the cells are present.

With regard to claim 39, the Examiner points out that this is a product-by-process claim that must set forth clear, distinct and positive method steps. The Examiner further states that claim 39 is unclear as to the purpose of reciting in parenthesis "main channel" in b) and "subsidiary channels" in c), and whether these terms are to be patentably limiting. The Examiner suggests that the terms in parenthesis be deleted, and that in line 5 before "supply," applicants insert -- main --, and in line 7, that applicants cancel "other" and insert --subsidiary--. The Examiner further states that in line 9, the meaning of "the end of the subsidiary channel/the ends of the subsidiary channels" is unclear as is "subsidiary channel/subsidiary channels" in line 11. The Examiner further asserts that there is no antecedent basis for "material" in line 10 and "the material stream" in line 11. The Examiner further asserts that the relationship of the material to the bone substitute

of claim 1 is unclear.

Applicants respectfully traverse this rejection. With regard to the Examiner's objections to claim 1, applicants explain that the bone substitute of the present invention does comprise three separate elements: a soft matrix, living cells and a setting matrix, although such elements are combined. The living cells are first embedded in the soft matrix, which contributes to the primary stability of the matrix. This soft matrix is formed by the fibrin suspension which is formed by mixing a fibrinogen solution and a thrombin solution (compare page 4, lines 2-11 of the description). The soft matrix in which the living cells are embedded is further mixed with a setting material comprising an aqueous solution of non-ceramic hydroxyapatite cement which forms the setting matrix. The setting matrix is responsible for the secondary stability. "Setting" means that the composition is no longer deformable but exhibits pressure resistance (page 6, line 6-11 of the description). Therefore, the setting matrix is one component of the bone substitute material which further comprises a soft matrix and the living cells.

With regard to the Examiner's objection to claim 8, applicants point out that claim 8 is directed to a bone substitute material as claimed in any one of claims 1, 4, 5 or 6, but which additionally comprises living angiogenic cells. Therefore, a bone substitute material is claimed which comprises a soft matrix, living cells, a setting matrix and additionally living angiogenic cells.

With regard to claim 39, applicants herewith amend such claim to address the Examiner's objections and to adopt the Examiner's suggestions.

In view of the above comments and amendments, applicants respectfully request the Examiner to reconsider and withdraw the rejections under § 112.

II. Claim Rejections – 35 USC § 103

Claims 1, 4-6, 8, 9, 12, 13 and 39 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Robey *et al.* (5,914,121) in view of Costantino *et al.* (document A08

on 1449 of 11/20/03) and Long *et al.* (5,972,703).

The claims are drawn to a bone substitute containing a soft matrix formed by mixing osteoblasts or precursors thereof with a fibrinogen solution and a thrombin solution, and a setting matrix formed by mixing the soft matrix with a setting material comprising an aqueous solution of non-ceramic hydroxyapatite cement.

According to the Examiner, Robey *et al.* disclose the preparation of human bone *in vivo* by implanting a composition containing cells, ceramic powder containing hydroxyapatite and fibrin, as shown for example, in claims 1-6.

Costantino *et al.* is said to disclose implanting a composition containing hydroxyapatite that sets *in vivo* for bone replacement. Long *et al.* is said to disclose (col. 13, lines 30-35) combining fibrinogen and thrombin to produce a fibrin clot. The capacity of osteoblasts to produce proteolytic enzymes that lyse the clot is overcome by using epsilon-amino caproic acid (col. 13, lines 36-40). Cells that differentiate into osteoblasts are used to treat bone disorders. The cells can be cultivated in the presence of collagen, fibrinogen and fibrin (col. 6, lines 40-45).

The Examiner's argument for obviousness is as follows. That is, it would have been obvious to replace the ceramic powder of Robey *et al.* with the hydroxyapatite composition suggested by Costantino *et al* to obtain its setting function *in vivo.* The Examiner further asserts that Long *et al.* would have suggested combining fibrinogen and thrombin to form fibrin by disclosing forming a fibrin clot by mixing fibrinogen and thrombin. Long *et al.* would have further suggested adding aminocaproic acid as in claim 4 to prevent osteoblasts from lysing the clot. Since Long *et al.* use cells that differentiate into osteoblasts to form bone, it would have been obvious to include osteoblasts or precursors thereof in the composition of Robey *et al.*

In response, applicants respectfully traverse the rejection, which is insupportable as a matter of law and fact. In order to sustain a rejection for obviousness, the Examiner must show all of the recited claim elements in the combination of references that make up the rejection. When combining references to make out a *prima facie* case

of obviousness, the Examiner is obliged to show by citation to specific evidence in the cited references that (i) there was a suggestion to make the combination and (ii) there was a reasonable expectation that the combination would succeed. Both the suggestion and reasonable expectation must be found within the prior art, and not be gleaned from applicants' disclosure. *In re Vaeck*, 20 USPQ2d 1438, 1442 (Fed. Cir. 1991); *In re Dow Chemical Co.*, 5 USPQ2d 1529, 1531 (Fed. Cir. 1988); *see also* MPEP §§ 2142-43 (Rev. 1, Feb. 2003). Applicants submit that the rejections do not meet this test.

In any event, a *prima facie* case of obviousness can be overcome by showing that (i) there are elements not contained in the references or within the general skill in the art, (ii) the combination is improper (for example, there is a teaching away or no reasonable expectation of success) and/or (iii) objective indicia of patentability exist (for example, unexpected results). *See U.S. v. Adams*, 383 U.S. 39, 51-52 (1966); *Gillette Co. v. S.C. Johnson & Son, Inc.*, 16 USPQ2d 1923, 1927 (Fed. Cir. 1990); *Bausch & Lomb, Inc. v. Barnes-Hind/Hydrocurve*, 230 USPQ 416, 419-20 (Fed. Cir. 1986).

Here, applicants admit that the present invention is a combination of elements and that such elements are taught in the art. However, the art does not show or suggest the combination, as claimed. Most importantly, nowhere in the prior art is there any indication why the person skilled in the art should replace one feature from one document and combine it with a feature obtained from another piece of prior art. As such, the Examiner's case is based upon impermissible hindsight and the proposed combination of art is improper.

Additionally, one could not arrive at the present invention by combining the art as the Examiner has done. Robey *et al.* disclose a composition comprising human marrow stromal fibroblasts (MSFs) in combination with a delivery vehicle. As delivery vehicle, hydroxyapatite/tricalcium phosphate (HNCP) powder is suggested. The compositions may further comprise fibrin glue (column 2, lines 63-67). In contrast, the claimed invention relates to a bone substitute material comprising living cells, at least some of

which are osteoblasts or precursors thereof (claim 1 b)). These are different from human marrow stromal fibroblasts used in Robey *et al.*

Additionally, Robey *et al.* disclose the use of a composition comprising hydroxyapatite/tricalcium phosphate particles which are already solidified and do therefore not represent a setting material. This can be seen from column 3, lines 56-58, that the delivery particles are hydroxyapatite/tricalcium phosphate (HA/TCP) powder, which particles are held together with a fibrin "glue". In contrast, the claimed invention is a bone substitute material comprising a setting matrix. The setting matrix is formed by mixing the soft matrix with a setting material comprising an aqueous solution of non-ceramic hydroxyapatite cement. This means that the bone substitute material comprises a component (setting material) which forms a solid structure after solidification.

A further difference between the disclosure of Robey *et al.* and the claimed invention is the function of fibrin. According to the present invention, the fibrin serves as support for the living cells and provides porosity and interconnecting holes within the setting material. In contrast, Robey *et al.* teach the use the fibrin for keeping together (glue) the already solid particles loaded with cells.

Therefore, in view of the above differences, one of skill in the art reading Robey *et al.*, would not have been directed to the claimed invention.

Costantino *et al.* disclose hydroxyapatite cement that can be shaped intraoperatively and which sets *in vivo* to an implant composed of microporous hydroxyapatite (first sentence of abstract). Major components of hydroxyapatite cement are (HAC) tetracalcium phosphate (TTCP) and dicalcium phosphate anhydrous or dicalcium phosphate dehydrate (DC) (page 381, first sentence of "Chemistry and Properties of HAC"). The material can be mixed with water, blood, saline, or weak phosphoric acid to create a "paste". The paste can then be used to fill facial-skeletal defects and can be contoured intraoperatively (page 380, right column, last full

sentence). It is not taught or suggested to include further ingredients in the HAG. Within the example ("Materials and Methods") disks of solidified HAG were implanted into cats. In contrast, the bone substitute material of claim 1 comprises at least a soft matrix, living cells and a setting matrix. The setting matrix is formed by mixing the soft matrix with a setting material comprising an aqueous solution of non ceramic hydroxyapatite cement. Further, the present invention relates to a bone substitute material which comprises a setting material, which sets after the application to the patient. Moreover, this material, which has the capability of setting within the body of the host, is mixed with living cells embedded in a soft matrix. Therefore, Constantino *et al.* fails to direct the skilled artisan towards the claimed invention.

Nothing in either Robey *et al.* or in Costantino *et al.*, respectively, guides one to combine their teachings. Even if this were not the case, one would not arrive at the invention through such a combination. Long *et al.* fails to cure this deficiency. Long *et al.* relate to methods, compositions and uses of bone precursor cells. Among these is a method of differentiating a bone precursor cell into an osteoblast. This method comprises cultivating the bone precursor cell in the presence of type I collagen, fibrinogen, fibrin, osteocalcin, or osteonectin (column 6, lines 37-40). Long *et al.* fails to suggest using these methods in preparing a bone substitute material or the use of osteoblasts or precursors thereof in a bone substitute material. Nothing in Long *et al.* would have motivated the skilled artisan to combine its teachings with Robey *et al.* and/or Costantino *et al.*

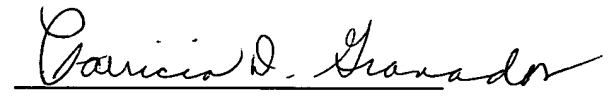
In view of the above arguments, applicants respectfully request the Examiner to reconsider and withdraw this rejection.

CONCLUSION

In light of the above amendments and comments, Applicants respectfully request that all rejections and objections be withdrawn and that a timely Notice of Allowance should be issued in this application. Should the Examiner have any questions, the Examiner is invited to contact the undersigned at the telephone number listed below.

Respectfully submitted,

Date: January 4, 2006



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